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Beyond Incremental Cost per QALY Ratios:

The Need for Alternative Methods to Evaluate Medical Interventions for Ultra-Rare Disorders

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Institute for Innovation & Valuation in Health Care

Michael Schlander, Silvio Garattini, Søren Holm

with Peter Kolominsky-Rabas, Erik Nord, Ulf Persson, Maarten Postma, Jeff Richardson, Steven Simoens, Oriol de Solà Morales, Keith Tolley, Mondher Toumi

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Discussion Paper

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Abstract

Regulatory policies have been adopted to encourage research and development (R&D) of treatments for orphan disorders, which have prompted concerns among payers about the costs that might arise with an increasing number of expensive treatments for rare and ultra-rare disorders (URDs). Inevitably, many drugs for URDs will fail to meet conventional standards for cost effectiveness. In particular in light of the high fixed (volume-independent) cost of R&D into new drugs, this issue will be more pressing with decreasing prevalence of any given disorder. The present paper sets out to explain the rationale underlying a recent expert consensus on these issues, recommending a more rigorous assessment of the clinical effectiveness of URDs, applying established standards of evidence-based medicine. This may include conditional approval and reimbursement policies, which should be combined with a firm expectation of proof of a minimum significant clinical benefit within a reasonable time. In contrast, current health economic evaluation paradigms fail to adequately reflect normative and empirical concerns (i.e., morally defensible "social preferences") regarding health care resource allocation. Hence there is a strong need for alternative economic evaluation models for URDs.

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Introduction

In the United States (US), in the European Union (EU), as well as in Japan, Australia and some other jurisdictions, legislation has been adopted to encourage the development of treatments for rare or "orphan" diseases [1]. Under this legislation, developers and manufacturers of so called orphan drugs to treat rare diseases benefit from a range of incentives, including reduced or waived licensing fees, extended market exclusivity periods, and in the U.S. and Japan, tax relief on development costs.

In theory, there are no distinct (sub-) categories of rare and ultra-rare disorders and treatments. Increasing rarity of a condition merely represents the end of a continuum, just like increasing severity and (in part) increasing comorbidities are continuous, not discrete phenomena. For policy-makers, it may nevertheless be pragmatic to define different categories of disorders and interventions, irrespective of the (absence of) theoretical merits of such an approach.

Definitions for "orphan disorders" typically include a criterion of prevalence or incidence and differ somewhat between jurisdictions. In the US, these are disorders with a prevalence of less than 200,000 affected persons (according to the Orphan Drug Act of 1983, and Orphan Drug Regulation of 1993) [1,2], in the European Union (EU), prevalence must be less than 1 per 2,000 (or less than 0.05 percent) of the population (according to EU Regulation CE No. 141/2000 of 2000) [1,3]. Strict criteria have also been set in Japan (fewer than 4 per 10,000, according to Orphan Drug Regulation of 1993) and Australia (less than 1.1 per 10,000, according to Orphan Drug Policy of 1997) [1,4,5]. In Taiwan and South Korea, prevalence thresholds have been set at less than 1 per 10,000 and 1 per 20,000, respectively [6].

No official definition of "ultra-orphan disorders" has yet been adopted globally. Rather, this informal subcategory was introduced by the National Institute for Health and Care Excellence (formerly, the Institute for Health and Clinical Excellence, and the Institute for Clinical Excellence; NICE), who applied it to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons [7,8]. The definition, albeit no less arbitrary than the definitions used for "orphan disorders", corresponds to the even more restricted prevalence criteria adopted by England's Advisory Group for National Specialist Services (AGNSS), that had been assigned the task of reviewing technologies for ultra-rare disorders (URDs) until April 2013. The qualifier required by AGNSS was less than 500 persons affected in England (i.e., approximately 1 in 100,000 of the English population) [9]. Publicly funded drug plans in the Canadian provinces of Alberta and Ontario also use very restrictive criteria, i.e., a prevalence of less than 1 per 50,000 in Alberta [10], and an incidence rate of fewer than 1 in 150,000 live births or new diafgnoses per year in Ontario [11].

As judged by the number of granted orphan drug designations, regulations designed to spur the development of treatments for rare disorders by providing economic incentives must be considered a substantial success [12-14]. Notably, the number of orphan medicines approved by the European Medicines Agency (EMA) and by the US Food and Drug Administration (FDA) has increased steadily since the enactment of legislation designed to mitigate the biopharmaceutical industry's high risks and uncertain rewards when investing in the development of treatments for rare disorders [15-17]. This success notwithstanding, there remains an ongoing need for new orphan medicines, given that the vast majority of rare and ultra-rare disorders – with their total number estimated at

approximately 7,000 – still await the development of effective treatment [17]. However, these policies will remain of limited relevance if any benefit to patients is hindered when subsequent reimbursement of treatments for rare and ultra-rare disorders is denied on grounds of their high incremental cost effectiveness ratios.

A number of agencies in charge of Health Technology Assessments (HTAs) have adopted cost utility analysis as a method of choice to determine the "value for money" offered by medical interventions [18]. For example, NICE expects that the use of drugs, to be recommended for reimbursement by the National Health Service of England and Wales, should not be associated with an incremental cost exceeding £20,000 to £30,000 per quality-adjusted life year (QALY) gained [19-21]. By adopting this approach, NICE followed the earlier models of Australia (with a benchmark in the range of AUS-$ 42,000 to AUS-$ 76,000 per life year gained) [22], New Zealand (with a reported cost effectiveness benchmark of NZ-$ 20,000 per QALY gained) [23], and Canada (with a suggested variable benchmark between CAN-$ 20,000 and CAN-$ 100,000 per QALY gained) [24].

It is easy to see that many drugs developed to treat URDs will not be able to meet the cost effectiveness thresholds stipulated by these and some other official regulatory bodies (cf. Tab. 1) [8].

***Table 1**: Preliminary cost per QALY ICER estimates by NICE (2008)*
These examples from England illustrate the mismatch between utra-orphan drug cost and conventional cost effectiveness benchmarks as adopted by NICE (i.e., 20,000£ to 30,000£ per QALY gained) [8].

Condition	Prevalence (England)	Product	ICER ("preliminary estimated £ per QALY")
M. Gaucher Type I and III	270	Imiglucerase (Ceredase[R])	391,200
MPS Type 1	130	Laronidase (Aldurazyme[R])	334,900
M. Fabry	200	Agalsidase beta (Fabrazyme[R])	203,000
Hemophilia B	350	Nonacog alpha (BeneFIX[R])	172,500
M. Gaucher Type I	270	Miglustat (Zavesca[R])	116,800

A key underlying reason for the failure of many orphan drugs to meet proposed – and, in some jurisdictions, actually applied – standards for cost effectiveness is that manufacturers need to generate revenues that allow them to recoup the cost of research and development (R&D), which also include the costs of gaining regulatory approval, from a small number of patients during limited periods of market exclusivity. This challenge inevitably results in high acquisition costs for these products on a per patient basis [25,26]. Key drivers of R&D costs are well understood and include, beyond out-of-pocket expenditures, the cost of failures (or "attrition rate", i.e., the proportion of development projects not leading to a marketable new product), regulatory obligations for phase I to III trials, development

times (averaging 12-13 years from discovery to marketing authorization) and the associated cost of capital [27-31]. Recent estimates accounting for these factors have indicated that the overall present value of R&D spending for a new molecular entity now might well exceed one billion US-$ on average [32], although some observers have taken different views and raised objections against the interpretation of these numbers [33,34]. From a commercial perspective, however, this staggering figure does not even reflect the additional market risks, which are illustrated by the highly skewed distribution of returns (i.e., the fact that a large number of newly developed products do not generate a positive return on investment) [30,32].

It is, of course, legitimate to ask whether, or to what extent, the development of medical interventions for rare and ultra-rare disorders benefits from special conditions. For example, early consultation with regulatory authorities and protocol assistance (as provided under EU regulation 141/2000 [1,3] and the U.S. Orphan Drug Act [1,2]) has been shown to improve the success rates of clinical development programs [35], and the number of patients included in clinical trials is typically smaller compared to more common diseases [12]. On the other hand, study logistics and patient recruitment may be more complex for rare and ultra-rare disorders, and mean development times appear to be similar for orphan and non-orphan development programs [36,37].

Nevertheless, given the largely fixed (i.e., independent from sales volume) nature of R&D costs, it seems plausible that the issue of not meeting conventional benchmarks for cost effectiveness will only increase in relevance with decreasing prevalence rates, especially with drugs developed to treat very small patient populations [26,38-40]. Consistent with this, drug

acquisition costs are inversely correlated with prevalence (cf. Fig. 1).

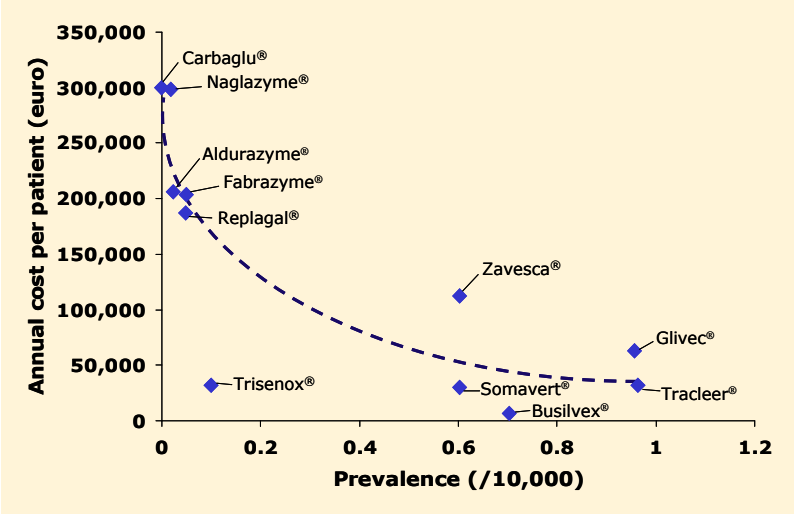

***Figure 1**: Increasing acquisition cost per patient with decreasing prevalence as a result of fixed (i.e., largely volume-independent) research and development (R&D) expenditures [26].*

Obviously there is a serious mismatch between reimbursement policies based on the logic of cost effectiveness, with cost per QALY benchmarks, on the one hand, and international policies designed to encourage research and development into rare and ultra-rare disorders and their effective treatment, on the other hand. There thus appears to be an unmet need for a coherent value framework reflecting all attributes of health technologies considered important by the public ("social preferences"), while at the same time remaining consistent with prior normative commitments as entailed by institutional and legal traditions. Such a framework should also enable to effectively address the

specific challenges that are posed by HTAs of interventions for the diagnosis and treatment of rare and ultra-rare disorders, combining fair access to effective interventions (for patients) with incentives for research, development, and "innovation" (for manufacturers). At the same time, given concerns about high drug acquisition costs per patient and potential impact in health care budgets [40,41], the framework should specify clear principles for setting limits (for policy makers and payers).

Most prominently in England, there have been attempts to protect the logic of cost effectiveness, built around cost per QALY benchmarks, against criticism by creating exemptions, thus isolating it from some of its most irritating implications. The introduction of an "ultra-orphan" category by NICE, as well as the introduction of a second special category, so called "*end-of-life*" treatments, can be interpreted as such a defensive move, responding to political and public pressures on NICE as a reaction to negative appraisals [7,8,42]. The need to create exceptions does, however, point to deeper issues regarding the generalizability of the "*logic of cost effectiveness*" as adopted by NICE. These may explain why estimating incremental cost per QALY ratios are not up to the task of evaluating drugs for rare and, especially, ultra-rare disorders, and may lead to recommendations that violate widely held fairness-related beliefs [43,44].

Objectives and Methods

To address this mismatch between regulatory incentives and reimbursement hurdles for URD treatments, the not-for-profit

Institute for Innovation & Valuation in Health Care (InnoVal[HC], Wiesbaden, Germany) convened an international expert workshop in Berlin, Germany, on November 08, 2012.

Objectives of the workshop were

1. to review the challenges that arise when applying conventional Health Technology Assessment (HTA) methodologies to medical technologies for ultra-rare diseases (URDs);
2. given these challenges, to seek expert agreement on the need for (improved or) alternative evaluation methods, ideally in the form of a consensus statement;
   and
3. in light of this analysis, to initiate discussion of improved or alternative evaluation methods, including the advantages and disadvantages of different options and possible ways forward.

After the workshop, two documents summarizing the discussion were drafted and circulated among the participating experts, whose comments were integrated in an iterative process, which led to the final consensus document [45]. In the present paper we, the group of scientists with relevant backgrounds in health economics, HTA, clinical pharmacology, and innovation management, set out to describe and explain the consensus achieved, and to outline potential ways forward that we agreed upon. In line with the timing of the workshop, an attempt was made to identify and discuss the relevant scientific literature available by November 2012 (effective cut-off date for inclusion).

Different potential levels of analysis were distinguished by the expert group, namely a focus on

1. the ***principles*** underlying the current evaluation framework,
2. the actual evaluation ***policies*** implemented by HTA agencies and regulatory bodies (primarily those concerned with pricing and reimbursement decisions), and
3. evaluation ***practice*** when principles and policies are applied to real-world problems. The third level would have to include case studies, including cases where existing regulation has been potentially misused.

The group agreed that discussion should initially focus on fundamental principles.

This was believed to be a reasonable approach, since policy implementation as well as evaluation practice (although clearly relevant dimensions) are hierarchically lower levels of analysis. The latter will have to be reviewed subsequently with reference to a set of prior higher-level guiding principles. Thus, as a first step, a situation analysis was undertaken in order to establish common ground for future deliberation.

Definitions

While recognizing the somewhat arbitrary nature of this cut-off criterion, the expert group agreed to focus on medical technologies targeting URDs (with a prevalence of less than 1 per 50,000), i.e., to exclude from further analysis the following related but different subject areas:

1. orphan disorders with a prevalence of less than 5 / 10,000 (or less than 1 / 2,000), but higher than 1 / 50,000;
2. cancer medicines (given their distinct characteristics, including the frequently observed gradual expansion of

indications, for example by moving treatments from third or fourth line to second line, combined, or adjuvant use in early-stage disease);

3. the specific challenges posed by emerging concepts of "personalized medicine";
4. also, for the time being, given the intended level of analysis (cf. above), potentially abusive commercial ploys such as "indication slicing" (of a biologically much broader and more prevalent condition, in order to obtain orphan designation) and other potential strategic instrumentarium of some manufacturers [17,46].

Further characteristics of URDs under consideration should include that the conditions are severe, are chronic, represent clearly defined biological entities, and, hence, are associated with a broadly accepted high unmet medical need – whereas the absence of alternative treatment options was not considered a necessary defining condition of an URD (as the broader criterion of "high unmet medical need" was believed to better capture the underlying rationale).

Subject of analysis were specific (unique) condition / treatment pairs fulfilling the criteria listed above. The typical case the workshop participants had in mind were treatments that are effective for one URD only (such as enzyme replacement therapies for hereditary lysosomal storage disorders). The panel shared the view that certain adjustments would probably be necessary when one drug works in more than one URD indication, but these adjustments were considered likely to be of a rather technical nature and, hence, were not explored in detail at the workshop as its primary focus was on the underlying fundamental evaluation principles.

IV

Results

Specific Challenges

The expert group recognized that "ultra-rarity" merely represents the end of a continuous spectrum of decreasing prevalence. Thus any prevalence threshold was seen as arbitrary in nature and justifiable for pragmatic reasons only. As a matter of principle, any considerations regarding the evaluation of URDs should be applicable to less prevalent conditions, too. The group agreed, however, that with increasing "rarity" a number of typical challenges must be expected when dealing with interventions for URDs. The most serious ones fall into one of two categories, (a) the need to establish evidence of clinical effectiveness, and/or (b) the need to demonstrate "value for money".

Establishing Evidence of Clinical Effectiveness

For several reasons, developing treatments for URDs is a more challenging, complex, and sometimes more risky endeavor than developing treatments for more common diseases, as

- less clinical / medical research is often available for URDs, resulting in a limited clinical understanding;
- there is usually a very small number only of physicians with specialized expertise, who are based in few specialized centers;
- there exist unusual difficulties to produce robust clinical evidence, for example, because of limited understanding of the natural history of URDs and because of the often limited availability of validated instruments to measure disease severity / progression;

- this, combined with difficulties to generate a large volume of evidence for URDs based on randomized clinical trials may lead to higher levels of uncertainty surrounding effect size estimators;
- significant hurdles exist when trying to identify and accurately diagnose patients with URDs;
- because the small number of patients are often geographically dispersed, multiple clinical trials sites must be established for only a few patients [36-38,47-50].

Further to this, ongoing post-marketing requirements must be met, including the creation of registries and risk management plans, which must be maintained globally for only a small number of patients.

As a consequence of the above, in a significant number of cases, the safety and efficacy profiles of orphan drugs have been incomplete, and often marketing authorizations were based on small scale studies addressing surrogate endpoints only [17,48,51,52].

Establishing "Value for Money" (Efficiency)

Further challenges are related to and extend beyond the sphere of generating evidence of clinical effectiveness. They are economic in nature and concern the efficiency or "value for money" offered by URD treatments:

- Across health care systems, there is a marked heterogeneity regarding institutional arrangements. This is mirrored by the situation that currently established methodologies to determine "value for money" vary internationally. A stronger utilitarian tradition (as for example in England) has generally led to a higher acceptance of "efficiency first"

evaluation principles, whereas stronger emphasis on a rights-based approach (and a corresponding legal tradition, as for example, in some continental European countries such as France and Germany) has made for a stronger reliance on approaches based on unmet medical need and on evidence of comparative clinical effectiveness for the allocation of health care resources [18,43,44,53,54].

- Neoclassical welfare theory built on the Pareto criterion for allocative efficiency is believed by many economists to represent "the theoretical high ground, […] although even the most committed Paretians acknowledge that distributional issues as well as efficiency issues need to be dealt with" [55]. Thus traditional economic theory, which uses maximum individual willingness-to-pay as universal measure of utility, has never gained real acceptance, and has even been notably unpopular, among health care providers and policy makers because of the wide-spread belief that basic necessities "such as life, health, and citizenship […] should be distributed less unequally than the ability to pay for them" – a view that has been referred to as "specific egalitarianism" [56].
- Accordingly the currently prevailing approach to the economic evaluation of health care programs does not consider utility but health gains as the central outcome used to assess the appropriateness ("efficiency") of health care expenditures. Usually this paradigm is directly linked to the assumption that the objective of collectively financed health schemes ought simply to be maximization of the aggregate health gain for the population covered by the scheme [57-59]. If and when health gains are "valued" (measured) in terms of quality-adjusted life years (QALYs), extrawelfarism then translates into QALY maximization, a normative

hypothesis that has been endorsed by extrawelfarists on grounds of an alleged "consensus in the literature." [60]

- From there it is straightforward to establish a ranking of medical interventions based on their efficiency as defined by their incremental cost per QALY gained (sometimes called QALY league tables, based on incremental cost effectiveness ratios, ICERs), implying a presumably increasing social desirability of services associated with decreasing ICERs. In practice, this approach translates into the adoption of some sort of a benchmark for the maximum allowable cost per QALY, which may be interpreted as the social willingness-to-pay for, or the shadow price of, a QALY. Interventions meeting this benchmark criterion will then be deemed "efficient" given a resource constraint [55,57,61].
- Claims of distributive neutrality notwithstanding ("a QALY is a QALY is a QALY, regardless of who gains or loses it" [62,63], a position termed by some economists as "QALY egalitarianism" [64]), this approach implies considerable constraints on the preferences to be taken into account [44,65,66]. Any contextual variable(s) – apart from individual health gain – potentially influencing the social desirability of (and hence the social willingness-to-pay for) health services would necessarily violate the basic assumption that all QALYs are created equal [67] – or simply need to be assumed away [68,69]. The focus on individual QALY gains in applied health economics also ignores health effects occurring in other people than the index patient, for instance in carers [55].
- If there were other objectives beyond the maximization of population health (which represents the restricted extrawelfarist version of the goal of allocative efficiency), such as the wish to be treated with dignity and respect, or

concerns about equity and fairness (for example, with regard to equality of access to care, or equal access for equal need, or more generally the recognition of differing moral claims of individuals, etc.), these quite obviously would either result in differential cost per QALY benchmarks as a function of these concerns, or might even require an entirely new evaluation paradigm. This issue has also been referred to using the notion of horizontal equity (i.e., the equal treatment of equals) versus vertical equity (i.e., the unequal but equitable treatment of unequals) [70]. As recognized early by philosopher economists campaigning to propagate the contribution of economics to applied ethics, "the principle of 'horizontal equity' … is … inconsistent with teleological maximizing." [71]

As noted earlier in the introductory section, many interventions for rare and ultra-rare disorders are unlikely (or altogether unable) to meet standard cost per QALY benchmarks. Hence, there is a need to examine the range of normative and empirical issues surrounding the application of the extrawelfarist logic of cost effectiveness (intended to serve as a criterion for allocative efficiency) for the prioritization of health care programs. In an attempt to escape from contentious interpersonal comparisons, politicians and health care policy makers in some jurisdictions, such as the United States and Germany, have deliberately decided to refrain from the computation of cost per QALY gained. In effect, priority setting is based on an assessment of comparative effectiveness by the Patient-Centered Outcomes Research Institute (PCORI) in the US [72] and by the Joint Federal Committee (Gemeinsamer Bundesausschuss, GBA) in Germany [73], respectively. At best, technical efficiency will be taken into account as a secondary criterion (e.g., methods guidance by the Institute for Quality and Efficiency in Health

Care, IQWiG in Germany, developed to avoid interventions across different disorders, and thus by design falling short of an economic analysis of allocative efficiency) [74].

With either approach, there remains the need to establish fair boundaries with regard to coverage (reimbursement) and pricing, and, by implication, with regard to access to medical technologies. This challenge is an inevitable consequence of the scarcity of resources available for health care, given the limited willingness of the public to be taxed (or the limited social willingness to pay for health insurance).

Valuation: Social Norms and Preferences

A number of specific normative as well as empirical ("positive") and technical problems arise when traditional HTAs include cost utility analyses, with QALYs as a measure of health-related outcomes (and their individual valuation) for URDs. In many ways, this can be interpreted as a reductionist simplification to react to the complexities of health care priority setting by attempting to reconstruct "social value" as an aggregate of individual utility only [75,76]. In applied health economic analysis, in turn, analysts take individual preferences almost always as a proxy for individual utility [77,78]. Individual preferences for health states, then, can be elicited either from patients (if measured ex post, "experienced utility") or, in practice more often after the consensus recommendations issued by the Washington Panel [79]), from a representative sample of the general population (if ex ante, "decision utility"), hereby employing a choice-based method such as the time trade-off or standard gamble [55,67,77-79]. This can be done directly, using health state vignettes, or indirectly, through the use of a validated health-related quality of life instrument [67]. All of

these methodological choices, as well as a number of further "technical" conventions broadly accepted and codified in health economic evaluation guidelines [44,45,55,67,79,80], are linked to normative implications. (Only some of the most salient ones will be briefly mentioned below, as this aspect – although clearly relevant – goes beyond the scope of the consensus to be explained here.)

Normative Ethics

The additive aggregation rule underlying the QALY maximization hypothesis corresponds to an (act) utilitarian calculus (sometimes referred to as "medical utilitarianism" [68], because it values health care services only if and when they improve people's health, and these health gains are considered as the one and only appropriate maximand). In effect, what matters under this rule is the distribution-independent sum total of population health only. The most serious normative issues arise, accordingly, when people are not only unwilling to subscribe to a pure utilitarian approach (in the case of traditional cost benefit analysis, firmly grounded in welfare economics), but likewise are also reluctant to adopt a quasi-utilitarian (in the case of "extrawelfarist" cost utility analysis) approach. The massive and continuously growing evidence that this may indeed be the case will be discussed in the following section ("*Empirical Ethics*").

Amartya Sen's objection against utilitarian welfare economics applies with equal force to extrawelfarism, too, i.e., that "each person deserves consideration as a person, and this militates against a distribution-independent view." [81] His critique resembles closely John Rawls' argument that distribution indifference does not take the distinction between persons

adequately seriously [82]. A person group's capacity to produce QALYs (i.e., individual health gain, valued or "weighed" by the strength of individual preference, multiplied by the number of persons benefitting from a health care program) counts as the only input, but the fate (at an extreme, even the death) of any one individual person (as a consequence of the resulting distribution of health benefits among persons and person groups) remains totally irrelevant– that is, as Sen put it, "if a person remains miserable or painfully ill, her deprivation is not obliterated or remedied or overpowered simply by making someone else happier or healthier." [81]

In contrast to utilitarianism, nonconsequentialist or deontological rights or "claims" based reasoning has a particularly strong tradition in medicine and health care [83]. Norman Daniels and others have extensively built and defended the argument that fairness requires to recognize a basic right of individuals to a "normal range of opportunities" to realize their plans in life. Insofar as disease and disability have a negative impact on this range of opportunities through impairment of normal functioning, this impairment should, according to this line of thought, serve as a "measure of the relative importance of health-care needs at the macro level" (however crude, as admitted by Daniels) [84].

Also the various legal systems, at both the national and at the supranational level, reflect deeply ingrained nonutilitarian value judgments, which cannot simply be sidelined in the present context. With particular reference to rare disorders, the following have all been cited as relevant to decisions determining levels of funding and commissioning [85]:

- human rights legislation, particularly Article 2 of the European Convention on Human Rights (ECHR), stipulating that "everyone's right to life shall be protected by law",
- as well as the United Nations Convention on the Rights of Persons with Disabilities,
- EU disability legislation,
- and, in the United Kingdom, the Equality Act of 2010 and UK "tort law".

Likewise, a recent Swiss consensus of stakeholders including physicians, payers (health insurance), and the research-based pharmaceutical industry, on the implementation of HTA in Switzerland [86] concluded that empirical preferences (neither individual nor social ones, see below) alone do not form a sufficient basis for decision-making on health care priorities; they rather need to be embedded in the context of a prior normative commitment. The consensus identified, in light of the national legal tradition, a number of fundamental principles guiding this prior commitment, namely, equality of rights, nondiscrimination (including that of persons with disabilities), special protection of the autonomy and the development opportunities of children, and, more recently, an emphasis on procedural justice [86].

While individual claims commonly correspond with moral duties [87], philosophers have argued that individual preferences *per se* – i.e., the notion that something is valuable to a person simply because she wants it – do not imply direct moral importance for others.[1] This line of thought inevitably leads to a serious challenge to the relevance of individual

[1] To illustrate the point with a few examples: a preference for food, shelter, or health care in case of need – all of these have a different moral quality than a preference for a luxury car, a soccer championship by one's favorite team, and so on, no matter what the strength of the latter may be [88,89].

preference satisfaction for social policy in general [88,89], and by implication, ultimately, no less so for health care resource allocation policy in particular. In the present context, discussing economic evaluation principles heavily relying on individual preferences for health states, it is important to note that preferences and needs are not equivalent [90]. This constitutes a clear contradiction to attempts to redefine "the concept of need", by asserting that "ill health does not necessarily indicate a need for health care, evidence of its cost-effectiveness being required to reach that conclusion," thus creating a tautology in order to justify claiming alignment between needs-based allocation and the logic of cost effectiveness using health gains valued by individual preferences as the maximand [91].

Empirical Ethics

If however social value transcends QALY maximization, one would expect that decreasing social desirability of medical interventions should be out of line with the ranking of interventions based on their increasing incremental cost per QALY gained, sometimes referred to as "QALY league tables" [92,93]. A few (admittedly extreme) examples may indeed suffice to illustrate the clash between the logic of cost effectiveness, when applied to questions of allocative efficiency, and widely held moral intuitions. The removal of tattoos [94] or the prescription of sildenafil for the treatment of erectile dysfunction in elderly men suffering from diabetes [95] would clearly meet the criterion of cost effectiveness as defined by maximum allowable cost per QALY gained, because in these cases strong individual preferences meet relatively low overall cost per patient. On the other hand, interventions near the end of life [42,66,96], including palliative care measures [96-99], and

interventions for people in double-jeopardy, i.e., those unfortunate enough to be afflicted with disabilities or other severe comorbidities [66,68,100], may face major obstacles to meet prevalent benchmarks of cost effectiveness. This list could be extended easily.

These examples suggest that the issue of how to properly evaluate interventions for ultra-rare disorders does pose much less of a singular problem (that, apart from temporary pragmatism, could be treated appropriately by way of exemption, in a way as NICE in the UK have tried to), and more so a symptom of deeper deficiencies inherent to the conventional evaluation paradigm. This violation of moral intuitions has led economists to wonder whether "economic evaluation [is] in touch with society's health values," [101] and more basically, "what values do the public want their health care systems to use in evaluating technologies?" [102]

If community values are to be respected, then a promising way to approach the issue of appropriate social objectives will be to use empirical evidence, instead of relying on the assumptions of economic welfare theory or its extrawelfarist variant [43,103]. The fact that most people apparently have preferences beyond narrow self-interest may indeed offer a partial explanation of the discrepancies between the prescriptive value judgments derived from an axiomatic theoretical framework and descriptive social values. For example, people have an interest in the social arrangements that shape the communities they live in. They are concerned with the well-being of other persons and frequently their decisions are shaped by their social preferences, leading to competition or cooperation. As citizens in a democratic society they might vote for a party that announced reforms that put them at a personal disadvantage because they believe these serve some greater public interest.

Important social preferences include reciprocity (or "reciprocal fairness"), inequality aversion and altruism, but also spiteful or envious preferences. However, neither spiteful nor altruistic preferences alone can explain why one and the same person may be willing to support others at a personal cost in one situation, while harming other people in other situations [104]. Social preferences cannot be fully understood without reference to norms and institutions [105]. To complicate matters further, they cannot omit the need for a prior normative commitment [84,106]. For example, a majority might vote for slavery or other immoral policies. Hence, not unlike individual preferences (which, for example, might be "evil, ignorant, adaptive, or otherwise mistaken preferences," [107] which may be based upon imperfect information, cognitive biases, prejudices, or simply sadistic tendencies [108,109]), social preferences need to be morally defensible, i.e., screened by ethical argument or "laundered" [76,110]. However, if both social and individual preferences were to be deemed irrelevant in a social policy context merely because of that limitation, the unsatisfying yet likely consequence by policy makers would be to revert back to attitudes of either nihilism or reductionism [75].

As a starting point, there is the need to recognize that the rapidly growing body of literature on social preferences clearly shows that the "QALY maximization hypothesis" must be considered "descriptively flawed" [111]. This conclusion has received particularly strong support from a systematic review of 64 empirical studies, which in most cases employed trade-off techniques in attempts to quantify the importance of attributes that have a bearing on fairness [111]. This observation in fact eliminates the normative foundation of universal cost per QALY benchmarks as a valid criterion of economic efficiency, unless analysts were prepared to deliberately ignore the question of

"what do people as citizens want from their health services?" [112], and replace it by an empirically falsified assumption regarding the objective of collectively financed health care. Rather, social preferences notably include equity concerns and a "sharing" perspective [113]. Before briefly discussing some of the most intriguing results on social preferences, it should be noted that many studies have been small, have looked at particular aspects in isolation, and need to be interpreted cautiously on account of methodological choices and framing effects. The next section will begin with a review of primarily health state related preferences and continue with a description of primarily person related dimensions. Finally, some provocative views of the public will be offered regarding the relevance of treatment costs. An important limitation of this section is the impossibility, in the present context, to explore in depth the moral relevance or defensibility and, hence, any potential need for "laundering" these preferences [87,106-110].

(a) Social preferences primarily related to health state

Perhaps the best documented and least controversial contextual variable is severity of the initial health state. In studies, people consistently show a strong preference to prioritize health care for the worse off, and this priority has been found to be largely (although not totally) independent from the improvement achieved by an intervention (i.e., the difference between the pre and post intervention health state as captured by the conventional computation of incremental QALY gains) [43,68,100,103,114,115]. Variations in study design have proven a challenge for recent attempts to quantify concerns for severity by transforming the observed effects into a social value function, despite consistently being found [116]. The priority for interventions targeting more severe initial health states quite

plausibly parallels the criterion of need proposed by moral philosophers [44,84,90].

A social preference has also been found for giving priority to those with more urgent conditions. The term "rule of rescue" has been coined to describe the moral imperative people feel to rescue persons facing avoidable death, largely irrespective of considerations of cost effectiveness. The moral relevance of being a visible victim – as opposed to being not identifiable – has been subject to debate and controversy [43,103,117-123].

In correctly applied cost utility analysis, the life of a permanently disabled patient would be valued lower than the life of a healthy person. This potential consequence raised concern and harsh controversy between philosophers and health economists [59,61,64,124,125]. Accordingly, in contrast to QALY-based valuation, the capacity to benefit seems to be relatively less relevant empirically, as people appear to value additional health gains lower, once a certain (however, not readily quantifiable) minimum effect has been shown to be achieved by an intervention [120,126-129]. This social preference reminds of the closely related legal norm prohibiting discrimination against persons with disabilities, and, by implication, persons in double-jeopardy, such as the chronically ill or the permanently disabled [43,85,86,103,130-133]. "Double-jeopardy" refers to the situation of a chronically ill or permanently disabled person who acquires an unrelated serious disease. She suffers a double jeopardy because she is disadvantaged by acquiring the serious disease, and she is additionally disadvantaged because treatment will not return her to full health. On top of that, under correct application of the extrawelfarist logic of cost effectiveness, she would be given a lower priority for intervention because, even if successful, the

intervention would only restore the previous state of illness or disability [130-133].

(b) Social preferences primarily related to patient attributes

Patient related attributes that have been found to influence the public's prioritization preferences include (younger) age, parent and caregiver status, and (non) smoker [134].

With regard to age, the majority of – albeit not all – studies to date have been supportive of assigning a somewhat higher priority to younger patients [115,135-144], but it has been found difficult by scholars to quantify the magnitude of this preference [143]. From a normative perspective, such an approach ("ageism") has been controversial [124,125,145-151]. It might however be justifiable on grounds of both equity and (utilitarian) efficiency arguments (irrespective of whether focused on health maximization or productivity). Within the field of health economics, Alan Williams has been the key proponent of the "fair innings" argument, which "reflects the feeling that everyone is entitled to some 'normal' span of health […] and anyone failing to achieve this has been cheated…"[147]. Similar arguments have been made by philosopher Daniel Callahan [152]. Compared to cost utility analysis, which considers future costs and outcomes, "the fair innings argument adopts a different standpoint and takes a person's whole lifetime experience of health as the appropriate concept to use when assessing inequalities in health…" [147]. The "fair innings" argument is not identical to but shows parallels with the view of "a decent minimum of health" as a prerequisite for individuals to have the opportunity to realize their life plans [84,90]. It has further been argued that Sen's capabilities approach might provide "a more natural justification of age

related access to health care" [151] – Of note, applying orthodox welfare economic principles might lead to the opposite answer, since one would have to expect average individual willingness-to-pay for a QALY to increase with increasing age [65]. This is because, technically speaking, decreasing marginal utility of both health and income would translate into changing marginal rates of substitution between life expectancy and income as a function of age: on average, income will tend to rise and remaining life expectancy will shrink with increasing age [65].

Other personal attributes influencing observed preferences for health care prioritization, such as social roles like parent and caregiver status, and (non) smoker can be broadly classified to fall into one of the following categories [134]: a person's relation to others (including relative socioeconomic status, family, contribution to community, criminal record, etc.) [120,135,153-155], individual life style choices contributing to ill health (such as nicotine or alcohol consumption, drug use, unhealthy diet, etc.) [120,135,155-158], and even self-related personal attributes (such as gender, sexual orientation and race) [135,155]. The potential moral relevance of such characteristics has been discussed extensively, for example by Jan Abel Olsen and colleagues [134]. In particular the latter group of examples reinforces the inescapable need of screening empirical preferences, in order to determine whether they are defensible against a prior normative commitment [76,95-97,134]. For these reasons, the "empirical ethics project" was suggested to be a process combining empiricism and normative theory, that should, it is hoped for, result in the "best available theory" at any given point in time [159].

(c) Social preferences, allocation rules and "rarity"

Finally, the decision rules of the logic of cost effectiveness will lead to "all-or-nothing" decisions on programs, depending on whether they fall above or below the cut-off line for efficiency (i.e., some maximum incremental cost effectiveness ratio, ICER, for a QALY gained). Studies however have shown that people are not at all indifferent to the fact that this way certain groups of patients would be entirely excluded from receiving health benefits; rather, there was a consistent willingness to sacrifice some efficiency in order to achieve equity in access [68,113,127,155,158]. Clearly most people were unprepared to abandon whole groups of patients [113,159,160], whereas the logic of QALY maximization, which is a prerequisite for the existence of cut-off thresholds or "benchmarks" separating efficient from nonefficient interventions, would necessarily result in a "winners take it all" solution [68]. Of note, a feature of a presumably "technical" nature associated with cost effectiveness analysis contributes to this outcome, namely the assumed perfect divisibility of programs and constant returns to scale [55,57,58,79] but implied indivisibility of resources across programs (i.e., one program is always better than another in terms of efficiency and therefore ranked higher) [68] (cf. below).

The question of the appropriate benchmark for the maximum allowable cost per QALY gained can only be addressed if one insists that such a universally applicable benchmark exists, and hereby is prepared to ignore the well-documented social values of the general public, as delineated above. Even then, the conventional decision rule based on ICER thresholds wouldn't be sufficient to determine the efficiency of resource use [161]. The primary reason for this deficiency is that (under the assumption of a limited budget [162]) "the threshold approach does not consider where the additional resources are to be taken

from, and hence the benefits foregone (or opportunity costs) by removing these resources from other uses." [163]

Often also the assumption of constant returns to scale [57,58] does not hold either. In the case of drug treatment, for example, there are almost always sharply diminishing costs per unit of output due to economies of scale, experience curve effects, and the typical high fixed / low variable cost structure of the biopharmaceutical industry [38,164-166]. Likewise, orthodox microeconomic equilibrium theory has distinct difficulties accommodating this cost structure, as it is often conveniently expressing both short-run as well as long-run marginal and average cost curves as U-shaped, i.e., with an upward slope [167,168]).

On the other hand, one "might expect that the marginal utility of QALYs diminishes with the size of QALY production" [169] – a possibility which has been assumed away by two linearity assumptions built into the QALY calculation algorithms, i.e., the "constant proportional trade-off" [170-172] and the strict proportionality of "social utility" and number of beneficiaries imposed by the additive aggregation rule [58,66,68,100,173].

All of this quite obviously has a direct bearing on the validity of cost-per-QALY-gained based evaluations of URD treatments. In particular, during ICER computation by definition patient numbers, or more generally, the absolute size of the numerator and the denominator, will cancel each other out. Hence, the ICER also will not indicate the size of the evaluated programs, and therefore the budget impact of a decision to fund a program within a collectively financed health scheme [169,174].[2]

[2] This has been referred to as "the silence of the lambda," with the "lambda" being the incremental cost effectiveness threshold [169,174].

These observations naturally led health economists to the question of whether we should "value rarity" [175]. Rarity of a condition, per se, is hardly an adequate reason for prioritization. It has been in fact been argued that the opportunity cost associated with the use of high-cost drugs for rare disorders will be substantial, and for the same amount of resources far more patients with more prevalent disorders could benefit [175,176].[3] It comes as no surprise that the (still very limited) evidence to date has been interpreted as indicative of limited support from the public to put special value on "rarity" as such [115,177,178].

In one Norwegian survey more than eighty percent of 1,479 respondents endorsed the statements, "all should have equal access to health care regardless of costs," and "patients with rare diseases should have the same right to treatment as others even if more expensive." When asked to choose between funding a rare or a common disease, about half of the respondents expressed indifference; forty-two percent favored dividing the funds available equally between the two disease groups, even if the common disease affected 200 patients and only 50 suffered from the rare disease. Economically this implies acceptance of a fourfold higher cost per patient for the rare compared with the common disorder. The study authors were however "reluctant to accept this interpretation as indication of a societal preference

[3] To quote, "the costs [for orphan drugs] will be borne by other, unknown patients, with more common diseases who will be unable to access effective and cost effective treatment as a result." [175] Rejecting the argument of limited overall budget impact, the same authors illustrated their position by pointing out that "… the cost should not be considered without reference to the value of what is foregone, £2.5m would pay for over 520 hip replacements" (with reference to the opportunity cost of a hypothetical drug costing £50,000 per year if there were only 50 patients to be treated) [176]. Indeed, hardly anyone would suggest that rare disorders, or patients afflicted with one of these conditions, can be likened to collectors' items, just as vintage cars or stamps are for some people.

for rarity," [177] because (among other potential reasons cited, including a preference for the middle option or "central tendency") the result could be a manifestation of aversion to choice [177,179].

A recent smaller Canadian study using a discrete choice method did not confirm respondents' willingness to pay more per life year gained for a rare disease than a common disease [178]. A choice-based UK social preference study also showed no societal values favoring expensive treatments for rare diseases [115]. At least at this stage, it would seem that the preferences elicited in the Canadian and UK studies were not meeting the criterion of being informed ones [71,109,110], as a sample of the general population participating in a survey cannot be expected to be familiar with the economics of biopharmaceutical R&D. However, in the absence of information about the cost structure of pharmaceutical R&D, respondents would be unaware of the resulting consequences for patients if willingness to reimburse remained unadjusted to prevalence. Reframing the alternatives, putting both the difference between horizontal and vertical equity [69,70] and the likely consequences for certain patient groups center stage [180], might well have led to an entirely different set of responses. Further to this, the focus on opportunity costs from an individual perspective rests on the shown on the "descriptively flawed" [111] assumptions that all QALYs are created equal, and that the sum of QALYs produced for the total population is the proper maximand. Owing to the fact that in economics opportunity costs are defined as value foregone, the appropriate perspective on costs will therefore deserve further attention and scrutiny [43].

(d) Social preferences and treatment costs

Empirical studies suggest that the importance of costs per patient may be overstated by conventional health economic evaluations [181], since cost-minimization, cost-effectiveness, cost-utility, and cost-benefit analyses, by definition, focus significantly on incremental cost per case. In contrast, the public does not appear to be prepared to deny patients treatment merely on the basis of cost – which constitutes a social preference closely related to principles of fairness or rights-based reasoning, in many respect similar to the dislike of "all-or-nothing" decisions, which also imply acceptance of opportunity costs (lost efficiency) in exchange for fairness (increased equity). As such, it does not necessarily imply valuing "rarity" per se.

Erik Nord and colleagues [181], in an Australian survey, collected 551 responses on a set of choices between two equally effective interventions for two groups of patients, the only difference being cost. Subjects were explicitly alerted to the fact that higher cost of treatment would mean that fewer patients could be helped, given that resources were limited. Nevertheless, more than 80 percent of the respondents rejected cost as a relevant criterion when selecting a medical technology. Remarkably, even when challenged by the researchers highlighting the budget limitation, still a solid majority of 70 percent preferred the equal priority option. When asked to explain their responses, survey participants emphasized that people cannot be blamed for contracting high-cost illnesses, that severity of illness should count rather than cost, and that people are equally entitled to treatment irrespective to cost." [181] Also when the implications of the different choices were illustrated by use of numerical examples, still 94 percent of the subjects challenged continued to prefer a budget allocation that did not maximize aggregate utility.

These results are not very dissimilar from some statements obtained in the Norwegian survey on orphan drugs mentioned above, such as "all should have equal access to health care regardless of cost" [177] – but Nord's study appears much more robust due to the repeated challenging of respondents and alerting them to the issue of opportunity costs. Corresponding findings were reported by Jose-Maria Abellan-Perpinan and Jose-Luis Pinto-Prades [127], who asked a Spanish convenience sample of respondents how they would allocate a budget between two treatments with the same outcome but the second of them twice as expensive as the first one. 74% of respondents preferred a 2:1 budget allocation, regardless of the opportunity cost [127]. These results are consistent with the findings obtained in studies reported earlier, for example, two studies examining social preferences for the allocation of scarce organs for transplantation in England [168] and the U.S. [160], and an Australian exercise in health care budget sharing [159].

In contrast, according to the logic of cost effectiveness, with its strong focus on ICER estimates and derived measures of efficiency, incremental costs per patient should be the yardstick [55,57,58]. For example, NICE has adopted the view that its decisions on technology coverage by the National Health Service (NHS) should be guided by cost effectiveness ("an additional QALY is of equal value regardless of other characteristic…"), whereas "the potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision." [182] Rather budget impact analysis at NICE is intended to primarily serve as an implementation tool [183]. However, from the viewpoint of a health care policy maker (or, in the case of the United Kingdom, a budget holding Regional Health Authority) total cost – or budgetary impact – may be relevant not only from a pure implementation

perspective [183]. After all, it is the impact on health care and social budgets that will determine opportunity costs at the program level [43,161,163,169,174].

These observations are of immediate relevance to the evaluation of interventions for URDs. Whereas costs per patient for URD treatment will necessarily tend to be (sometimes much) higher than the cost per patient for more common disorders [40,41,184], as discussed earlier, most technologies for URDs have a limited overall budget impact only.

While this is usually true for individual treatments, the combined budgetary impact of the health service costs for many URDs may be more profound: budget impact for rare disease drugs in Europe was around 3.3% of total drug spending in 2010, with available data indicating a range from 0.75% (for The Netherlands, 2006) to 6.6% (projection for Europe, 2016, upper extreme scenario) [185-190]. Owing to the expiry of market exclusivity for an increasing number of products, it has been predicted that European sales growth of orphan drugs should level off through 2020, after having reached a peak of 4.6% (range between 3.0% and 6.6%, according to sensitivity analyses) of total drug sales [189]. URD treatments will represent only a (presumably small) part of the entire group of "orphan drugs."

Some Methodological Issues

Although this is not the focus of the present paper, it seems worth mentioning a few salient methodological problems that many analysts have treated as purely "technical" issues.

Central to the extrawelfarist logic of cost effectiveness is the idea of some benchmark for the monetary value of a statistical life year adjusted by a utility weight representing the individual

preference for (health-related) quality of life (or quality-adjusted life year, QALY). One way to think about this value is as the shadow price of a QALY in a given health scheme, subject to a fixed budget constraint. This however cannot be determined empirically as it would require perfect information about the cost effectiveness of all interventions funded [55,161,163]. An alternative way to interpret this benchmark is as the social willingness-to-pay for a QALY [55,67].

Unfortunately, there are several different economic methods available to estimate this value – and even when one excludes the human capital approach, the median values obtained vary greatly by study type, depending on the method chosen. In a review published in 2000, for example, these values ranged from a median of US-$ 93,000 in revealed preference non-occupational safety studies over a median of US-$ 161,000 in contingent valuation studies to a median of US-$ 428,000 in revealed preference job risk studies [191]. Thus the choice of method is a major determinant of the cost effectiveness benchmark obtained, revealing all currently used benchmarks [18-24] as entirely arbitrary *ad hoc* standards [192].

Major parts of the health economic literature, addressing (1) the process of ranking intervention based on their cost per QALY (the "league table" approach [92,93]) as well as (2) possible solutions to approximate a valid benchmark over time [193], treat this problem as a presumably technical one. This way they gloss over the more fundamental normative issues intrinsic to the application of a quasi-utilitarian calculus to the allocation of health care resources [44,68,81,100,124,125,180].

Measurement problems also arise regarding the choice of generic index instrument to measure the utility weights required for health state valuation, as a prerequisite for the

computation of QALYs. The available instruments differ in their descriptive systems, the number and levels of dimensions and items, the valuation method used, and their sensitivity to dimensions, and hence the QALY differences resulting from a change in certain health states may also differ greatly depending on the choice of instrument [67]. Not very surprisingly, convergent validity of the instruments has been shown to be relatively low, with instruments explaining only 41 to 64 percent of each others' variance according to the two five-instrument comparison studies published to date [194,195].

A substantial number of further issues has been "resolved" by standardization via the introduction of conventions and additional assumptions, which not only collectively impose a large number of largely *ad hoc* restrictions on the evaluation function, but at the same time represent normative choices (in effect, value judgments) under the guise of technical discussion[4] [43,44,55,66-68,78,79,100,103,112,180,196]. Taken together, they characterize the currently prevailing health economic evaluation paradigm, i.e., logic of cost effectiveness using cost per QALY benchmarks, as a pragmatic "technocratic" attempt [197] to solve the complex problem of allocating health care resources fairly, and must cast serious doubt on its status as a coherent scientific theory.

[4] These choices include, but are not limited to, who should be asked when eliciting utility values for health states, whether to adopt an *ex ante* or *ex post* perspective, which method to use (time trade-off, standard gamble, etc.; choice of multiattribute utility instrument, etc.), the appropriate perspective for costing and which costs to include, how to determine productivity loss for analysis, the treatment of future unrelated costs, and many more [44,55,78-80,100,112,196].

Some Key Observations

At this point it can be concluded that

- QALYs, conceptualized as a preference-based measure of individual health-related outcomes combining quality and length of life, seemingly fail to capture the full social value of URD technologies; hence they need to be complemented by or replaced with alternatives that include societal preferences, such as concerns for equity in access to treatment;
- current (cost per QALY) ICER thresholds used for cost-effectiveness (or more precisely, cost-utility) analysis are largely arbitrary and particularly inappropriate when used to evaluate URD technologies; their application may lead to positively unethical conclusions that might deprive patients with URDs any chance of access to effective care, thus conflicting with fairness- and rights-based considerations;
- the very existence of these thresholds (outside the confines of the narrow extrawelfarist framework) depends on the validity of the QALY maximization hypothesis, whereas systematic reviews of the literature have convincingly shown that this assumption is "descriptively flawed", i.e., these thresholds do not capture well-established social preferences beyond to the quasi-utilitarian (health outcomes) maximization principle (which, by design, is "distribution-blind");
- attempts to apply modifiers to account for severity of disease (so called "equity" or "severity weights" [198-201]) in economic assessments of technologies for URDs have not fully reflected the large number of contextual variables, and cannot solve the underlying issues with regard to fair chances to have access to effective treatment.

Perspectives

Collectively, the findings and observations summarized above underscore the need for an evaluation paradigm capturing and reflecting social preferences better than the conventional logic of cost effectiveness. Alternative approaches should fare better than the conventional approach in tests of so called reflective equilibrium, examining the social acceptability of priority rankings of health care programs [82,202-204]. Accordingly, the considered moral judgments about justice in particular cases should carry weight [205]. We predict that this will be accompanied by far-reaching implications for the evaluation of URDs.

Evidence of Clinical Effectiveness

The starting point of any value analysis can only be clinical benefit. In their comprehensive review of the first decade of orphan drug legislation in the European Union, Roberta Joppi and colleagues (2013) [17] found that many orphan drugs were approved with evidence of surrogate endpoint effects only. In the absence of sufficiently strong evidence for some minimum significant and clinically relevant benefit [206,207], which however is not easily quantifiable [208,209], there is no basis for any robust value determination.

While recognizing the challenges associated with developing clinical interventions for URDs, the panel agreed that evidence for improvement of surrogate endpoints only should be no more than an interim attitude (in contrast to recent demands to further ease requirements for marketing authorization [210]),

providing a basis for provisional approval and reimbursement, in order to ensure patients' fast access to new technologies. It should be linked to managed entry schemes such as "coverage with evidence development" agreements in order to incentivize further research [211,212].

There is a need for ongoing R&D for highly innovative and life-saving products for URDs, in order to increase clinical disease understanding and produce robust evidence on the clinical effectiveness of interventions [17,47-49,213]. Clinical benefit needs to be proven not promised. In general, the current state of affairs regarding orphan medicines and the available evidence of clinical effectiveness is not satisfactory [17,47,48,51,52]. Yet there are examples that demonstrate that it is feasible to prove relevant patient benefits [17,52,214].

Even at a prevalence rate of a given condition as low as 1/50,000 (the URD qualifier), there will be about 10,000 patients in Europe. Thus it should be possible to set up multinational randomized controlled trials, including between 500 and 1,000 patients, designed to show relevant clinical endpoint benefit. If necessary, such trials might be supported not-for-profit research centers such as the "*European Clinical Research Infrastructures Network*" (ECRIN) initiative devoted to promote multinational studies [215,216].

Perspectives on Cost

As stated earlier, the cost per patient will tend to be higher with decreasing prevalence. Budget impact, however, can be looked at in various different ways.

1. One prevalent view (consistent with the efficiency-first approach advocated by conventional health economics)

is that budget impact should not be relevant to coverage decisions, which ought to be based on incremental cost effectiveness [55,175,176]. For example, NICE has taken the position that budget impact analyses should not form part of the decision making process; rather, they should be used as a tool aiding UK Regional Health Authorities in implementing NICE guidance locally [182,183].

2. Given that ICERs by design provide no information on the dimension of a program, as the size of the numerator and the denominator cancels out (the so called "silence of the lambda") [161,163,169,174], health care policy makers are concerned with the budget impact of adopting a technology (consistent with the notion of "affordability"), and methods have been proposed by health economists on how one might combine incremental cost effectiveness and budget impact into one metric [217].
3. If a social value perspective (instead of a focus on individual utility) was to be adopted in a consistent manner, then there could be simultaneous implications for the definition of social opportunity cost (or value foregone) [43], with social value being driven by the existence of a program (i.e., for example the value people might attach to living in a society that does not simply abandon certain groups of patients, who are unfortunate enough to suffer from a high cost illness) and opportunity cost by its budgetary impact. This would obviously shift the focus from cost per patient to cost on the program level, which indeed reflects the perspective of a real-world decision maker. Incidentally, this would also correspond to recent trends in commercial value

management, which have been characterized by s shift from price maximization to revenue management for maximizing corporate profit [218].

4. Finally, a more pragmatic approach might combine rights-based thinking in terms of a desire to offer fair chances to receive effective treatment also to patients with URDs with the realities of pharmaceutical R&D and its fixed cost structure; resulting in the implementation of price / volume trade-offs as realized, for example, in France [219].

Valuation Principles

According to recent reviews, orphan drugs often are not supported by favorable cost effectiveness data, and in some cases, cost effectiveness information simply does not exist [184,220]. This might at least in part be explained by the shortcomings of the prevailing evaluation paradigm discussed above, and in some cases by the impossibility to meet standard benchmarks for cost effectiveness. It has also been argued that, if those benchmarks were considered inappropriate for rare and ultra-rare disorders, producing cost effectiveness estimates might become superfluous [220]. This leaves policy makers without useful economic guidance when they have to make defensible decisions on market access, reimbursement, and appropriate use of interventions for URDs [40,41,221,222].

Hence there is a need for evaluation principles that better reflect the public's social preferences (compared to the logic of cost effectiveness using cost per QALY benchmarks). Examples for such approaches, which hold promise to overcome at least some of the weaknesses of the conventional logic, include (but are not limited to),

- methods combining traditional cost effectiveness with budget impact analysis [217], or cost value analysis by means of adjusting cost per QALY benchmarks according to multiple contextual variables [201];
- using alternatives to QALYs as a measure of benefit, such as "capability-adjusted life years" [223-225];
- cost value analysis using the person trade-off method [100], or cost value (or social utility) analysis using the relative social willingness-to-pay (RS-WTP) instrument [226];
- a multi criteria decision analysis (MCDA) framework [46,227-230].

All of those should be rigorously assessed for their potential to improve on the currently predominant standard, which is still represented by conventional cost utility analysis. Given the limitations of the conventional approach, the strengths and weaknesses of each of the alternatives should be explored with high priority. The group believes that investigating this way forward should take precedence over the continued application of an obviously deficient evaluation model for URDs. Needless to say, the group further believes that the constraints on the application of the conventional logic of cost effectiveness as well as any alternative evaluation principles should, in principle, also apply to the assessment of interventions for "non-ultra-rare disorders". These constraints should allow health care policy makers to make well-informed decisions, setting limits fairly.

IV

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